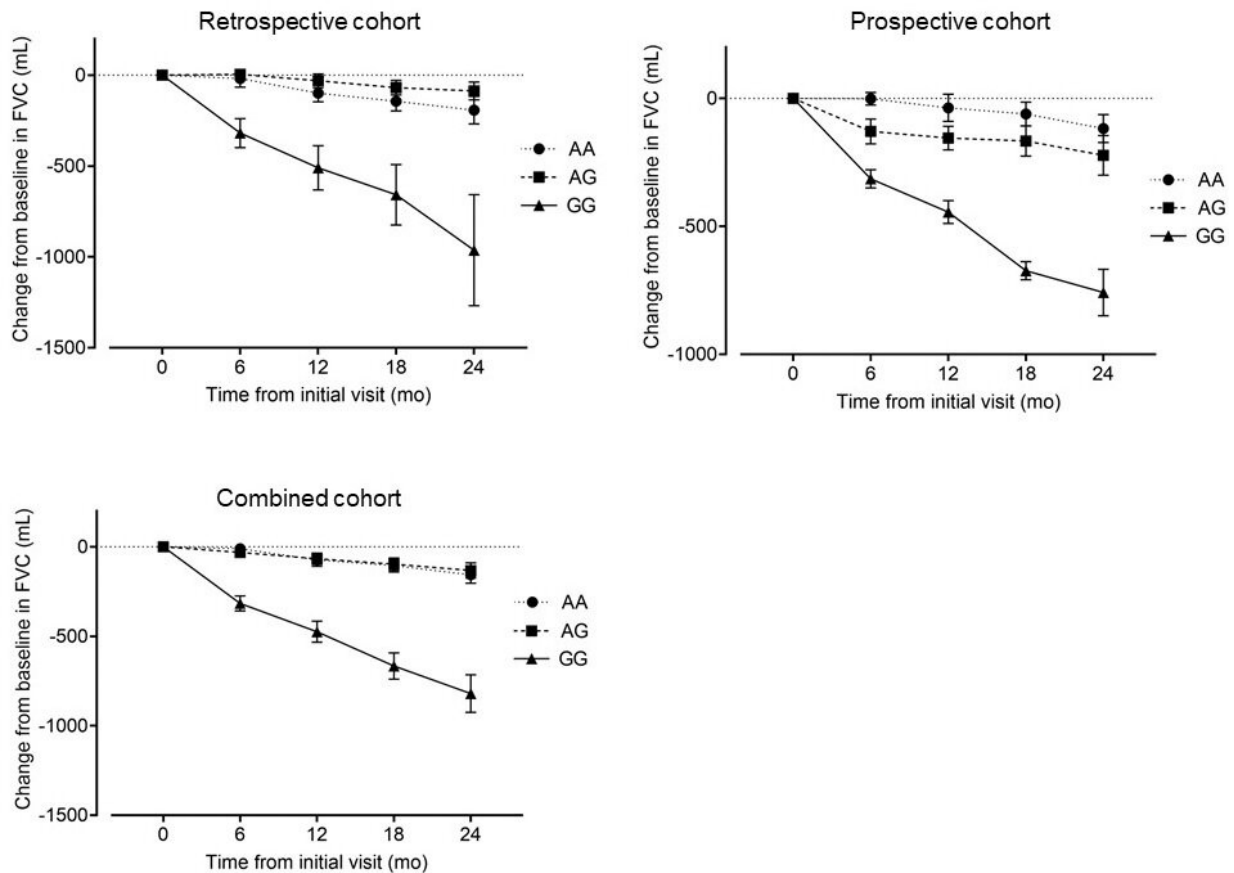


Genetic variant linked to prognosis of chronic hypersensitivity pneumonitis

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The GG genotype showed significant decline in FVC over 2 years compared with AA and AG. Importantly, these results were consistent in the retrospective and prospective cohort as well as in the combined cohort. Credit: Department of Respiratory Medicine, TMDU

Chronic hypersensitivity pneumonitis (CHP) is a long-term lung condition where the interstitial tissue surrounding the alveoli (air sacs) of the lungs becomes inflamed and develops "fibrosis", or scar tissue. It occurs when susceptible individuals inhale allergens. The full process and circumstances underlying the development of the condition are currently unknown, but it is thought to have a strong genetic component.

Now, in a study published in the journal *Chest*, a team at TMDU have discovered a link between the condition and a variant in a gene known as TOLLIP. This gene encodes TOLLIP (Toll-interacting protein), which acts as a negative regulator of innate immunity. The innate immune pathway is the body's first defense against pathogens and is also involved in the response to allergens. The researchers took a cohort of patients with CHP and looked at the [genetic variation](#) in single-nucleotide polymorphisms (SNPs), places in the genome where variation occurs at a single position in the DNA sequence.

"We found that one [genotype](#) of an SNP known as rs5743899 was associated with a higher degree of immune activation and an increase in the cellular signaling responses leading to fibrosis. This causes a progressive reduction in lung function in patients with CHP", says lead author Shinji Katayanagi. The patients with the "GG" genotype of this SNP showed more severe disease progression and a steeper decline in the forced vital capacity (FVC), a test of [lung](#) function that measures the maximum amount of air able to be expelled from the lungs after a maximum inhalation.

The team observed that patients with the GG genotype had lower levels of TOLLIP in the lungs compared with patients with the other genotypes. They also showed increased fibrotic activity in the lungs in these patients, as they detected both a higher level of the phosphorylated form of a protein called Smad2, a major component of the fibrotic pathway, and increased levels of periostin, a marker of fibrosis. "It

seems that the functional changes caused by the TOLLIP variant are associated with rapid FVC decline in CHP due to the dysregulation of fibrosis-related signaling pathways such as Smad/TGF- β and NF- κ B signaling", says senior author Yasunari Miyazaki.

The identification of the association between this genotype of the rs5743899 SNP and a poorer prognosis of CHP could prove invaluable for assessing patients at their initial diagnosis, and for guiding their treatment.

More information: Shinji Katayanagi et al, Alternative Gene Expression by TOLLIP Variant Is Associated With Lung Function in Chronic Hypersensitivity Pneumonitis, *Chest* (2021). [DOI: 10.1016/j.chest.2021.08.052](https://doi.org/10.1016/j.chest.2021.08.052)

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